REMARKS

Claims 1-4, 6, 11, 12 and 39 are currently pending in the application. New claims 50 and 51 have been added with this Amendment. Namely, claim 50 recites the deleted subject matter compound from amended claim 11, and claim 51 recites the gadolinium complex of the compound of claim 51. Thus, claim 1-4, 6, 11, 12, 39, 50 and 51 are currently pending.

Claims 2, 6, 11 and 39 have been amended by deleting the limitation "- or a single bond." Claim 11 was further amended by deleting the recited compound name (redrafted as claim 50).

The pending claims were objected or rejected over various informal, § 112, or § 103 grounds. Applicants will respectfully traverse each ground below.

A. Informal Objections

Claims 2, 3, 6, 11, 12 and 39 were objected to based on the reasoning that these claims teach that m' may be zero, which has the same meaning as A1 is a single bond, as previously cited in the claims. Office Action, p. 2. To simply expedite prosecution, and not for any reasons related to patentability, Applicants have amended claims 2, 6, 11 and 39 by deleting the phrase "- or a single bond." As such, Applicants have not relinquished or surrendered any equivalents or scope of coverage as a result of this amendment. Thus, this issue is moot and withdrawal of this objection is respectfully requested.

B. Applicants' Claims Satisfy § 112, ¶ 1.

Claims 2, 3, 6, 11, 12 and 39 were rejected under 35 U.S.C. § 112, ¶ 1 based on the reasoning that the specification did not disclose the limitation that m may be zero. Office Action, p. 3. Applicants respectfully traverse. The original specification and examples as filed teach that m may be zero. For example, compounds 10-12 in Table 1 (p. 41), which represent the compounds of Examples 1, 2 and 3, can be drawn as shown in structure identified as 3-12 on p. 39 of the specification. In these structures, it is clear that m equals zero (*i.e.*, there is no CH_2

present connecting the tetraaza-cyclododecane ring to the carbonyl group). As such, Applicants' claims reciting that m can be zero are supported by the specification as original filed and withdrawal of this rejection is respectfully requested.

C. Applicants' Claims Satsify § 112, ¶ 2

Claims 11 and 12 were rejected under 35 U.S.C. 112, ¶ 2 based on the recitation of various alternatives for the claimed formula despite already reciting the specific compound name as well. Office Action, pp. 3-4. Applicants have amended claim 11 by deleting the specific compound name. Thus, claims 11 and 12 are definite and withdrawal of this rejection is respectfully requested. Applicants note that claims 50 and 51 have been added to claim this specific compound.

D. Applicants' Claims Are Nonobvious

Claims 1-4, 6 and 39 were rejected under 35 U.S.C. § 103 as being unpatentable over the cited reference Society of Magnetic Resonance in Medicine, Book of Abstracts, 8th Annual Meeting, August 12-18, 1989 ("Society"). Office Action, pp. 4-5. Applicants respectfully traverse.

The Examiner stated that the Society's compound, PA-DO3A, differs from the species of the instant invention in that the hydrogen atom of PA-DO3A is replaced by a methyl group.

The Examiner reasoned:

> "As homologues with such similar structures would be expected to have similar properties and utility, it would be obvious to one of ordinary skill in the art to make various homologues of PA-DO3A, including the methyl compound of the present invention, for use in the study of lipophilicity in mice."

Applicants respectfully disagree.

First, Applicants' claims are not "homologues" of the Society compound. For example, the additions and substitutions on the aromatic moiety of the claims at issue are not additions of

CH_2 groups to the Society compound, PA-DO3A. Furthermore, as demonstrated below, Applicants' claims cover compounds and complexes with unexpectedly superior properties than PA-DO3A.

Second, there is no teaching, suggestion or disclosure in the cited reference to make Applicants' specific compounds.

Third, the Examiner has failed to show why someone of skill in the art would be motivated to make such substitutions. Only the use of hindsight, which is not permissible, could possibly lead one to make Applicants' specific invention. The Examiner does not point to any art that would provide the motivation to make Applicants' invention from PA-DO3A. For this reason alone, the obviousness rejection should be withdrawn.

Indeed, any actual motivation provided by the cited reference leads away from Applicants' invention. The cited reference cannot provide motivation to make to the PA-DO3A complex and obtain Applicants' claimed subject matter. One of ordinary skill in the art would read Society and determine that PA-DO3A produces residual ^{153}Gd in the liver, a very undesirable effect since Gd is toxic. One of ordinary skill in the art would clearly and indisputably be led to the other complexes disclosed in the reference, not PA-DO3A and not Applicants' substituted aromatic rings. Thus, the actual motivation provided by the reference leads away from Applicants' invention.

The cited reference also lacks any disclosure of utility whatsoever, further demonstrating a lack of motivation to make substitutions. This fact alone precludes a finding of obviousness. The cited reference does not disclose any relevant properties of the Society complex -- the unsubstituted ring is never shown to have the utility of Applicants' claimed complexes. Furthermore, Applicants' claims are directed in their preambles to a "diagnostic agent," a

property never disclosed in cited reference. In fact, the only relevant properties of the Society complex can be learned from a hindsight review of Applicants' own specification and they are found to be wanting when compared to Applicants' invention.

Fourth, the rejection should be withdrawn because there are more substantive differences between the compounds than a mere substitution. The instant invention differs from the Society complex in that Applicants have, for example, a substituted aromatic amide moiety of the formula found on page 9, line 13, of the specification at one of the nitrogen atoms of an amino carboxylate ligand. The Society's compound contains an unsubstituted aryl moiety. The Society compound is discussed in Applicants' specification on page 7, about line 19, among other places. As demonstrated throughout Applicants' specification, Applicants' substituted aromatic amide moiety is unique and offers unexpectedly enhanced properties and advantages over the Society's compound.

One such property is high relaxivity. Relaxivity, as defined in the specification starting on page 2, line 33, is the effectiveness, per mole of complex, of altering the relaxation times of the nuclei being imaged. Generally, the greatest possible relaxivity is a highly desirable and fundamentally important property of these contrast agents — the higher relaxity produces better MRI images. Table I on page 41 of the specification compares the relaxivities of various Gd complexes, including the Society's and Applicants'. As seen in entry 7 of Table 1, the Society's PA-DO3A unsubstituted aryl moiety compound has a T, relaxivity of only 4.1. In contrast, Applicants' compounds, with their substituted aromatic amide moieties, table entries 10-12, have relaxivities ranging from 5.4 to 5.9, roughly 35-50% higher than the Society's. In fact, relaxivities were discovered to be especially high only in the substituted aromatic amide compounds of the instant invention.

Another result of Applicants' invention is its ability to bind to biomolecules. By virtue of the R_1 and R_2 substituents on the aromatic amide moiety, which are absent in the cited reference, the instant invention has the ability to bind to, among other things, monoclonal antibodies for use with radiotherapy and imaging. Monoclonal antibodies are beneficial in that they can be used to target radionuclides to cancer or tumor sites with great specificity. As stated on page 16, lines 11-13 "the compounds of this invention wherein R_1 is other than hydrogen are then linked to monoclonal antibodies or fragments thereof". Such a linkage imparts biological specificity to the metal chelate complex. Such binding can occur only with the existence of the R_1 and R_2 groups on the aromatic amide moiety. This enables Applicants' invention unparalleled specificity and efficacy in radiotherapy and in imaging over the prior art.

Finally, a further advantage of Applicants' substituted aromatic amide moiety is enhanced water solubility. Blood is primarily composed of water. For radiographic contrast agents to work, they must be soluble in blood, thereby enabling the agents to be transported to specific organs without the fear of precipitation and organ failure. On page 7, lines 22-24, it is noted that the Society's compound, when used to chelate a paramagnetic compound such as Gd for use in magnetic resonance imaging, was found to exhibit poor water solubility. Poor water solubility is avoided in the instant invention because, unlike ionic contrast agents, Applicants' compounds are non-ionic with favorable water solubility.

In light of Applicants' arguments and amendments, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejections and objections.

No additional fees are believed due. However, if any additional fees are necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-0540.

Dated: March 2, 2004

Respectfully submitted,

KRAMER LEVIN NAFTALIS & FRANKEL LLP
Attorneys for Applicants

By: _____

Donald L. Rhoads, Reg. No. 34,705
Albert B. Chen, Reg. No. 41,667
Kramer Levin Naftalis & Frankel LLP
919 Third Avenue
New York, NY 10022
(212) 715-9100